REMARKS

The Office Action dated December 11, 2001 has been received and reviewed. Claims 1-13, 15 and 18-23 are pending in the present application. All pending claims stand rejected. The application is to be amended as previously set forth. An Examiner's Interview was conducted on Wednesday, May 29, 2002 and the claim amendments made herein are in accordance with the same. All amendments and claim cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. **Declaration**

The declaration was objected to due to non-initialed and/or non-dated alterations made thereto. The declaration was further objected to because it erroneously stated that the specification is the specification for PCT NL/00156 rather than a continuation of PCT NL/00156. A substitute declaration in compliance with 37 C.F.R. § 1.67(a) is submitted herewith to correct the inadvertent errors in the previously filed declaration. Applicants respectfully submit that the objections to the declaration have been obviated and, accordingly, request their withdrawal.

2. **Reference Not Considered**

The van Oosterhout document cited on the IDS submitted September 22, 2000 was not considered by the Examiner because inadequate citation information was given. The cited document is actually a manuscript was submitted for later publication and subsequently published. Submitted herewith is a Supplemental IDS identifying the citation information for the publication.

3. **Claim Rejections Based Upon van Oosterhout et al.**

Claims 1-8, 10-13, 15 and 18-23 were rejected under 35 U.S.C. § 102(b) or § 102(a) as being anticipated by van Oosterhout, Y.V.J.M. et al., *Suitability of a Cocktail of CD34 and CD7 Ricin A-Immunotixins for in vivo Treatment of Acute Graft-Versus-Host Disease*, Thirty-Ninth Annual Meeting of the American Society of Hematology, San Diego, California, USA, December 5-9, 1997; BLOOD 90 (10 Suppl. 1 part 2), November 15 ,1997, 376B; ISSN: 0006-4971, page 376B, column

2, paragraph 4439 (hereinafter the "van Oosterhout reference"). It is stated in the Office action that the date of publication is necessary to determine the appropriate statutory section on which to base the rejection. As stated in the previous section, the publication date of the reference is November 15, 1997.

Attached hereto are declarations under 37 C.F.R. § 1.132 from each of the named inventors traversing the grounds for rejection based on attribution. As stated in the declarations, the van Oosterhout reference is attributable to the applicants herein and, thus, the van Oosterhout reference is not applicable against the instant application. Further, the van Oosterhout reference was published less than one year prior to the present application for U.S. Letters Patent. Accordingly, applicants respectfully request that the van Oosterhout reference be removed and the rejection based upon such reference be withdrawn.

4. **Claim Rejections Based Upon 35 U.S.C. § 102(b) and § 103(a)**

Claims 1-5, 7-13, 15, 18, 19 and 21-23 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 89/06967 to Scannon et al. (hereinafter "Scannon".) Claims 1-13, 15 and 18-23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Scannon in view U.S. Patent 6,261,535 to Thorpe et al. (hereinafter "Thorpe"). As none of the art of record teaches, either inherently or expressly, nor suggests, the composition and/or method as recited in the amended claims of the present application, applicants respectfully traverse the rejections.

As amended herein, independent claim 1 recites a pharmaceutical composition for eliminating or reducing the number of unwanted CD3 and/or CD7 positive cells. The composition of amended claim 1 "consists essentially of" first molecules directed against CD3 and second molecules, distinct from the first, directed against CD7, wherein at least one of the first and the second molecules (e.g., the second molecule) includes a toxic moiety. As amended herein, independent claim 15 recites a method of treating a disease state in a subject believed to be suffering therefrom, the disease state comprising at least one of Graft vs. Host disease, graft rejections, T-cell leukemias, T-cell lymphomas, other lymphomas, other CD3 and/or CD7 malignancies, autoimmune disease, and infectious immune diseases. The method of amended claim 15 comprises administering

to the subject an amount of a pharmaceutical composition consisting essentially of first molecules directed against a CD3 positive cell and second molecules, distinct from the first molecules, directed against a CD7 positive cell, wherein at least the second molecules include a toxic moiety. Neither Scannon nor Thorpe teaches, either expressly or inherently, compositions or methods having the combination of elements recited in independent claims 1 and 15, as amended herein.

Further, neither Scannon nor Thorpe suggests compositions or methods having each of the elements recited in amended independent claims 1 and 15, respectively. Immunotoxins comprising both molecules directed against CD3 (or CD3 positive cells) and molecules directed against CD7 (or CD7 positive cells) yield unexpected and surprising results. First, as discussed at the interview, a composition comprising molecules directed against CD3 has been found to be especially effective against cells having CD3 receptors even when such molecules are not coupled to toxic moieties. This is because CD3 has been found to have some antigen presenting cell (APC) blocking functionality (*see*, page 5, lines 24-28). Second, a composition comprising molecules directed against CD7 has been found to be especially effective against cells having CD7 receptors because such receptors are present not only on T-cells but also on NK-cells as well. Further, NK-cells have been found to play a role in certain disease states, namely Graft vs. Host Disease (GVHD) (*see*, page 10, lines 21-31). Third, it has been found that administration of compositions comprising both molecules directed against CD3 and molecules directed against CD7, when both include a toxic moiety, generates a surprising effect in the treatment of GVHD relapse. Specifically, it has been found that, even if GVHD relapse occurs, it is treatable with a low dose of corticosteroids. This is in contrast to previous data concerning the treatment of GVHD relapse with the same low dose of corticosteroids (*see*, page 5, lines 29-37).

As such, it is respectfully submitted that neither Scannon nor Thorpe, nor the combination thereof, teaches or suggests a composition and/or method as recited in amended independent claims 1 and 15, respectively. Accordingly, applicants respectfully submit that the rejections of claims 1 and 15 based upon these references have been overcome. As each of claims 2-8, 10-13 and 18-23 depend, either directly or indirectly, from one of claims 1 and 15, the rejections of these claims have been overcome as well for at least the above-cited reasons. Applicants respectfully request

withdrawal of the § 102(b) and § 103(a) rejections of claims 1-8, 10-13 and 18-23. Claim 9 has been canceled by way of this amendment and, thus, the rejections of this claim have been rendered moot.

5. **Miscellaneous Remarks**

Independent claims 1 and 15 have been amended to include, in the respective preambles thereof, the transitional phrase "consisting essentially of". As discussed at the interview, such a phrase represents partially-closed terminology wherein the claim is open only for inclusion of un-recited elements that do not "materially affect the basic and novel characteristics of the claimed invention." *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409,412 (Fed. Cir. 1984). *See also, AFG Indus. v. Cardinal IG Co.*, 239 F.3d 1239, 1245, 57 U.S.P.Q.2d 1776 (Fed. Cir. 2001) (reiterating the definition of "consisting essentially of" as defined by 750 F.2d at 1574). As such, independent claims 1 and 15 are open only to those un-recited elements that do not materially affect the basic or novel characteristics of the claimed composition and method, respectively.

Exemplified in the present application is an immunotoxin combination having two murine monoclonal antibodies, at least one of which is conjugated to a toxic moiety. Immunotoxins are being developed based upon the viewpoint that native antibodies, in general, suppress but do not efficiently eliminate their target cells. Therefore, with immunotoxins, a toxic moiety is conjugated to the antibody to dramatically improve on the antibody's intrinsic killing efficacy. At the present time, the most effective toxins are of plant or bacterial origin (*e.g.*, pseudomonas exotoxin, diphtheria toxin and ricin). Consequently, it does not have much impact whether the antibodies themselves are of murine or human origin. This is in contrast to non-conjugated monoclonal antibodies which are either "humanized" or of fully human origin to enable long-term administration.

The statement that the nature (*i.e.*, animal or human) of the antibody component in an immunotoxin is of minor therapeutic significance is supported by a number of observations. First, the compositions disclosed in the present application are administered as a single course of four infusions within a one-week time period. No anti-composition antibodies are to be expected within this short time frame. In practice, only one in seven subjects treated demonstrated a slightly elevated

titer of antibodies directed against the toxic moiety of the composition. This is in direct contrast to the follow-up Scannon work, *i.e.*, Byers et al., wherein it is reported that 6 in 23 subjects treated with a murine-conjugated immunotoxin demonstrated anti-immunotoxin antibodies. *See*, Byers et al., *Use of Anti-Pan T-Lymphocyte Ricin A Chain Immunotoxin in Steroid-Resistant Acute Graft-Versus-Host Disease*, 75 BLOOD 1426-1432, No. 7, April 1, 1990. The low incidence of anti-immunotoxin antibodies may be explained by the effective removal of T-cells (the primary target of the composition), which are vital to B-cells for mounting an effective antibody response.

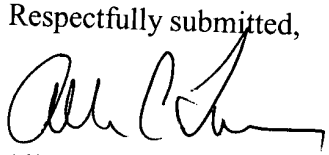
Second, anti-immunotoxin antibodies do not prevent immunotoxin efficacy *per se*. Several examples exist of immunotoxins generating clear clinical response in the face of circulating anti-immunotoxin antibodies. For instance, clinical trials with Ontak, the first immunotoxin approved by the FDA for clinical use, nicely illustrate this point. Ontak consists of a cell-targeting protein conjugated to mutated diphtheria toxin. Administration of Ontak has been shown to generate objective clinical responses, both in patients with and without circulating antibodies to the diphtheria toxin.

CONCLUSION

Claims 24-25 have been added to the present application. It is respectfully submitted that claims 24- 25 are supported by the application as filed and do not introduce new matter herein and, based upon the interview, should certainly be allowable.

In view of the present amendment and the above remarks, claims 1-8, 10-13, 15 and 18-26 are believed to be in condition for allowance and an early notice thereof respectfully is solicited. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



Allen C. Turner
Registration No. 33,041
Attorney for Applicants
TRASKBRITT, P.C.
P. O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: (801) 532-1922

Date: June 11, 2002
ACT/TLW/

Enclosures: Supplemental IDS
Check No. 2521 in the amount of $180.00
37 C.F.R. § 132 Declarations
Substitute Declaration and Power of Attorney
Petition for Three-Month Extension of Time
Check No. 2520 in the amount of $920.00